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REVIEW article

Suzetrigine mechanism, efficacy, and clinical implications: A narrative review

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Abstract: Acute pain, especially in postoperative and trauma areas, continues to be a substantial clinical problem all around the world, and this has been made worse by the opioid crisis as well as the drawbacks of the current non-opioid analgesics. The recent approval by the FDA of Suzetrigine (Journavx®) in January 2025 as the first-ever non-opioid analgesic aimed at the NaV1.8 sodium channel has opened new paths in pain management. Suzetrigine works only on NaV1.8 in the peripheral pain-sensing neurons, giving the patient targeted relief from pain without central nervous system (CNS) side effects or the risk of addiction. This paper sums up the newest clinical trial results (NAVIGATE-1 and NAVIGATE-2), real-world evidence, and regulatory frameworks to give a complete account of Suzetrigine's pharmacology, clinical efficacy, safety profile, and potential to change acute pain treatment. While Suzetrigine showed a statistically significant and clinically relevant reduction in pain during Phase III trials, its use on a long-term basis for chronic pain and in other fields still has to be studied. This review furthermore evaluates the factors that make it difficult to approve such medicine, like doctors' education and the cost, and at the same time, it encourages the research and policy changes that will be needed to harness the full power of Suzetrigine.

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Introduction

The International Association for the Study of Pain (IASP) characterizes pain as “a negative sensory and emotional experience that is linked to or stands for the actual or possible damage of tissues” [1]. The intricate nature of pain, in its physiological as well as in its psychological, social, and cultural dimensions, brings with it the consequences for the patient and the quality of life that are most pronounced. Acute pain, which usually accompanies surgery, trauma, or medical treatment, is the most common and disabling condition with a worldwide effect on the lives of a lot of patients. It is estimated that more than 80.0% of surgical patients worldwide experience acute pain, and this scenario results in longer hospital stays, higher healthcare costs estimated at $560-635 billion yearly in the United States alone, and up to 20.0% of cases turning into chronic pain due to the treatment being ineffective [2]. In treating pain that is moderate to severe, opioids are still the mainstay, even though their potency is acknowledged and accompanied by a very high risk of dependence, misuse, and overdose [3, 4]. Prescribing more than needed and misappropriation have aggravated the opioid crisis, which has been responsible for over 100,000 overdose deaths in the U.S. in 2024; thus, indicating the urgent need for a shift in pain pharmacotherapy methods [5]. Even though COX-2 inhibitors and peripheral nerve blocks have been regarded as non-opioid analgesics, they still provide only partial relief and are frequently withdrawn due to adverse effects like gastrointestinal toxicity and cardiovascular risks, or their limited effectiveness in pain management during severe pain scenarios [6]. The crisis surrounding opioids has brought to light the pressing requirement for the discovery of new pain-relieving methods that are safe, effective, and non-addictive. As a result, the U.S. Food and Drug Administration (FDA) approved Suzetrigine (Journavx)® in January 2025, the first novel non-opioid analgesic for moderate-to-severe acute pain in more than two decades [7, 8]. Suzetrigine exerts its effect through selective inhibition of the voltage-gated sodium channel NaV1.8 in peripheral pain-sensing neurons, thereby blocking pain signal transmission without engaging the central nervous system or conferring addiction liability [3, 9]. The utilization of peripheral targeting reduces the side effects of the central nervous system, and at the same time, it corroborates the IASP’s multimodal pain management guidelines, thereby encouraging the use of a balanced approach consisting of the combination of pharmacological and non-pharmacological interventions [1]. This narrative review presents a comprehensive analysis of the drug’s pharmacology, clinical efficacy, safety profile, and regulatory context of Suzetrigine, especially focusing on its capability to bring about change in the management of acute pain. Emerging evidence is being synthesized by us to provide guidance for clinicians regarding the integration of Suzetrigine into practice while at the same time pointing out the areas that need further investigation.

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Methods

This narrative review was performed with the help of a systematic search through electronic databases like PubMed, Google Scholar, and the FDA website for articles published in the years 2024 and 2025. The search terms that were used included "Suzetrigine," "Journavx®," "NaV1.8 inhibitor," "non-opioid analgesic," and "acute pain management." The selection of the relevant clinical trials, regulatory guidance, peer-reviewed articles, and prescribing information was made according to their coverage of Suzetrigine's mechanism, efficacy, safety, and clinical implications. A formal meta-analysis was not performed, as this is a narrative synthesis of the available evidence. For capturing comprehensive information, we have given priority to high-impact journals and have included gray literature from regulatory bodies in order to reflect the real-time developments in the clinical adoption of Suzetrigine.

Mechanism of action

The role of NaV1.8 in pain signaling: Voltage-gated sodium channels are the main components in the control of neuronal electrical activity and the propagation of pain signals. Of the nine identified NaV subtypes, NaV1.7, NaV1.8, and NaV1.9 are mainly expressed in the pain-sensing neurons of the peripheral nervous system [3, 9]. NaV1.8 is especially heavily present in dorsal root ganglion neurons and indeed mediates the transfer of pain signals [9, 10]. NaV1.8’s tetrodotoxin-resistant properties enable sustained action potentials in nociceptors, amplifying inflammatory and thermal pain responses, as evidenced by genetic knockout models showing profound analgesia without motor deficits [11]. NaV1.8 is not expressed centrally, thus making it an ideal target for peripheral analgesics [9, 12].

Suzetrigine’s selective inhibition of NaV1.8: Suzetrigine selectively inhibits NaV1.8 by binding to the second voltage-sensing domain (VSD2), stabilizing the channel in a closed state and blocking sodium influx [9, 10]. Unlike non-selective sodium channel blockers, Suzetrigine’s high specificity (>31,000-fold over other NaV subtypes) avoids neurotoxicity and cardiac arrhythmias [9, 13]. Electrophysiological assays confirm >30,000-fold selectivity over NaV1.5 (cardiac isoform), supporting its cardiovascular safety in human iPSC-derived cardiomyocytes [14].

State-dependent inhibition and safety: Suzetrigine exhibits “reverse use-dependence,” whereby inhibition diminishes with repeated depolarizations, contributing to its favorable safety profile [3, 13]. Preclinical and clinical data confirm the absence of addictive potential or dependence [3, 9]. This state-dependent modulation preferentially inhibits hyperexcitable nociceptors during pain states while preserving normal sensory function [15].

Clinical Efficacy

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Phase III trial results: NAVIGATE-1 and NAVIGATE-2: The pivotal Phase III trials NAVIGATE-1 (abdominoplasty) and NAVIGATE-2 (bunionectomy) demonstrated Suzetrigine's superiority over placebo on the primary endpoint of time-weighted sum of pain intensity differences over 48 hours (SPID48) [3, 7]. Although Suzetrigine was not superior to hydrocodone/acetaminophen on SPID48, its non-opioid mechanism and absence of addiction risk position it as a valuable alternative [3, 16]. Subgroup analyses revealed consistent efficacy across age, sex, and BMI strata, with notable benefits in opioid-naïve patients [3].

Real-world evidence and broader applicability: A Phase III single-arm study supported efficacy in both surgical and non-surgical acute pain settings across a broader population [17]. Early post-marketing data suggest sustained pain relief in emergency department trauma settings with high patient satisfaction [16].

Adverse effects and safety: Suzetrigine is well tolerated, with <1.0% discontinuation due to adverse events. Common mild-to-moderate events include pruritus, muscle spasms, rash, and increased creatine kinase [3, 7]. No sedation, respiratory depression, or withdrawal symptoms were observed [7, 18]. As a CYP3A4 substrate, dose adjustment may be required with strong inducers/inhibitors [19]. Safety beyond 14 days, in pregnancy, or in multimodal regimens remains to be established [7].

Discussion

Clinical implications of Suzetrigine's approval: The FDA's approval of Suzetrigine (Journavx®) in January 2025 represents a landmark advance in pain management amid the ongoing opioid crisis [2, 7, 8]. For decades, clinicians have faced a difficult choice: highly effective opioids carrying substantial risks of addiction and overdose, or non-opioid alternatives that were often inadequate or burdened by serious toxicities [2, 3, 6]. Suzetrigine's highly selective blockade of the NaV1.8 sodium channel in peripheral nociceptors eliminates central nervous system engagement and, consequently, addiction liability - a genuine breakthrough in analgesic therapy [3, 9]. From our perspective, this approval signals the beginning of precision analgesia, in which targeting specific molecular pain pathways (such as NaV1.8) allows personalized treatment that respects the heterogeneity of pain experiences and may help reduce disparities in underserved and low-resource regions [20].

Comparative efficacy and place in therapy: The NAVIGATE-1 and NAVIGATE-2 Phase III trials demonstrated statistically significant and clinically meaningful pain reduction with Suzetrigine compared with placebo, with a rapid onset (median time to ≥30.0% pain relief of 4.0 hrs versus 8.0 hrs) [3, 16]. Although Suzetrigine did not outperform hydrocodone/acetaminophen on the primary endpoint of SPID48, its non-addictive profile makes it a compelling alternative [3, 16]. We believe Suzetrigine is best

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positioned as a first-line agent for moderate-to-severe acute pain in patients at elevated risk of opioid use disorder (e.g., those with prior substance-use history, elderly individuals, or respiratory compromise) and as a core component of multimodal analgesia to minimize opioid exposure, fully aligning with current FDA guidance [7, 16]. Its favorable safety and equivalence in short-term efficacy make it particularly suitable for enhanced recovery after surgery (ERAS) protocols, where opioid-sparing approaches have already reduced postoperative opioid consumption by 30.0-50.0% [21]. We anticipate rapid incorporation into guidelines from organizations such as the American Society of Anesthesiologists in the near future.

Safety and tolerability: Suzetrigine exhibited an excellent tolerability profile in clinical trials, with mild-to-moderate adverse reactions (pruritus, muscle spasms, rash) and a discontinuation rate below 1.0% [2, 3]. Compared to opioids, no sedation, respiratory depression, or withdrawal symptoms were reported [2, 18]. Being a CYP3A4 substrate, the possibility of clinically relevant drug-drug interactions exists; however, these are manageable through dose adjustment or therapeutic monitoring, just like with other established CYP3A4 substrates [19, 22]. Even though there were no cases of severe hepatic injury in short-term studies, it is still crucial to have longer-term and real-world data, especially for those with liver dysfunction or taking multiple medications [2, 19]. Post-marketing surveillance and patient registries will be critical for detecting rare events, especially in vulnerable populations and across diverse skin types, where dermatological reactions may be underreported. The FDA's recent emphasis on extended post-approval monitoring for non-opioid analgesics reinforces the need for robust pharmacovigilance programs [7].

Regulatory and policy implications: Suzetrigine's approval reflects a deliberate shift in regulatory philosophy driven by the opioid crisis and the urgent need for safe, non-addictive analgesics [7, 8]. The FDA's Overdose Prevention Framework and new draft guidance on non-opioid drugs for both acute and chronic pain highlight a commitment to accelerated development of safer alternatives [7, 23]. While reliance on relatively short-term trial data (48 hrs efficacy, 14 days safety) enabled rapid access, it also underscores the importance of rigorous post-marketing studies to confirm long-term safety [2, 3]. In our view, closer harmonization between FDA and EMA requirements - ideally through the International Council for Harmonization — would expedite global availability, especially in low- and middle-income settings where opioid alternatives remain scarce [24]. Suzetrigine's success is likely to stimulate investment in next-generation NaV1.8 inhibitors and related ion-channel therapeutics.

Barriers to adoption: Despite its good features, several obstacles can limit its wide-ranging adoption. The price of Suzetrigine is way over that of generic opioids, which could be a reason why it won't be accessible in health systems with limited resources [16, 18]. A lot of doctors do not know about NaV1.8 pharmacology and its medical

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implications, which means that there is a strong need for specific continuous medical education and refreshed treatment guidelines [7, 16]. The difference in regulations between the FDA and EMA may slow down getting approval elsewhere apart from the US [23, 25]. Furthermore, patients' past exposure to opioids might lead them to have certain expectations about non-opioid options, which would require education and decision-making support to get them to finally accept the treatment [16]. To tackle this issue, we suggest implementing value-based pricing linked to opioid reduction results and the quick creation of short educational modules to boost acceptance.

Call to action: The unlocking of Suzetrigine’s full capability is going to need a joint effort of researchers, clinicians, professional societies, payers, and policymakers. Long-term safety studies, trials in chronic pain states, and special population (pediatric, geriatric, pregnant patients) evaluations should be considered as the priority. The development of international registries and the improvement of post-marketing surveillance will be the essential real-world evidence providers. Remarkably, the equitable global access will require the pricing strategies and regulatory harmonization to be fair.

Conclusion: Suzetrigine (Journavx®) is the first non-opioid pain management drug that has ever existed. Its selective NaV1.8 inhibition, fast action, and good safety profile make it a favorable option for both patients and other healthcare providers. However, more studies are needed to check its long-term use and the ability to treat chronic pain, but Suzetrigine's new method of operation and being non-opioid can be said to be the future of acute pain therapy. Interestingly, previously, many pain medications were believed to be very effective but eventually withdrawn from the market because of hidden dangers or poor results. Suzetrigine's triumph will depend on its acceptance in the system, not only on its effectiveness in trials but also on educational, policy, and research support. Ultimately, Suzetrigine exemplifies how targeted innovation can restore balance to pain care, offering hope amid the opioid shadow.

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Authors' contribution: NMS & ARA conceived and designed the study. NMS collected the data ad contributed to data analysis. Both authors drafted the manuscript, reviewed and approved the final version of the manuscript.
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